JACC: HEART FAILURE
VOL. 5, NO. 1, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.11.009

EDITORIAL COMMENT

Primary Prevention of Sudden Arrhythmic Death in Dilated Cardiomyopathy

Current Guidelines and Risk Stratification*

Eloisa Arbustini, MD,[a] Marcello Disertori, MD,[b] Jagat Narula, MD, PhD[c]

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS IN DILATED CARDIOMYOPATHY: LEFT VENTRICULAR EJECTION FRACTION ONLY?

With the exception of selected cases, the left ventricular ejection fraction (LVEF) is currently the sole basis for the selection of patients with nonischemic dilated cardiomyopathy (DCM) for implantable cardioverter-defibrillator (ICD) therapy for the primary prevention of sudden cardiac death (SCD) (1). However, data collected over the past decade have demonstrated that the LVEF criterion does not justify the best use of ICD therapy. The majority of patients who receive ICD devices on the basis of LVEF ≤35% not only may not need ICD intervention but could also be exposed to the devices' side effects. However, a smaller proportion of patients even with LVEF >35% (and therefore not suitable for ICD implantation) might experience SCD and hence should have received ICDs. The recently reported results of the randomized DANISH (Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischemic Systolic Heart Failure on Mortality) trial (2) have uncovered some of the limitations of current LVEF-based guidelines. In 1,116 patients with symptomatic, nonischemic DCM (LVEF ≤35%) randomized to ICD versus non-ICD arms and followed for a median of 67.6 months, ICD therapy did not result in a significant reduction in death of any cause compared with usual clinical care. On the basis of already existing observational data and now with at least 1 randomized clinical trial, it has become important that the risk stratification of nonischemic DCM be reconsidered and that other markers be used for better characterization of high-risk patients. The ventricular fibrosis identified by cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) has been evaluated as a promising tool for the targeted stratification of SCD in nonischemic DCM (3).

ICD IN DCM: LVEF + LGE ONLY?

In this issue of *JACC: Heart Failure*, Di Marco et al. (4) present a systematic review and meta-analysis of the association between LGE-based myocardial scar and the risk for ventricular tachyarrhythmia in patients with DCM, wherein 2,948 patients (reported in 29 studies) were followed for an average of 3 years. The arrhythmic endpoint was defined as sustained ventricular arrhythmias, appropriate ICD intervention, or SCD. LGE was present in 44% of patients. The investigators included only observational studies because of the paucity of randomized trials in DCM.

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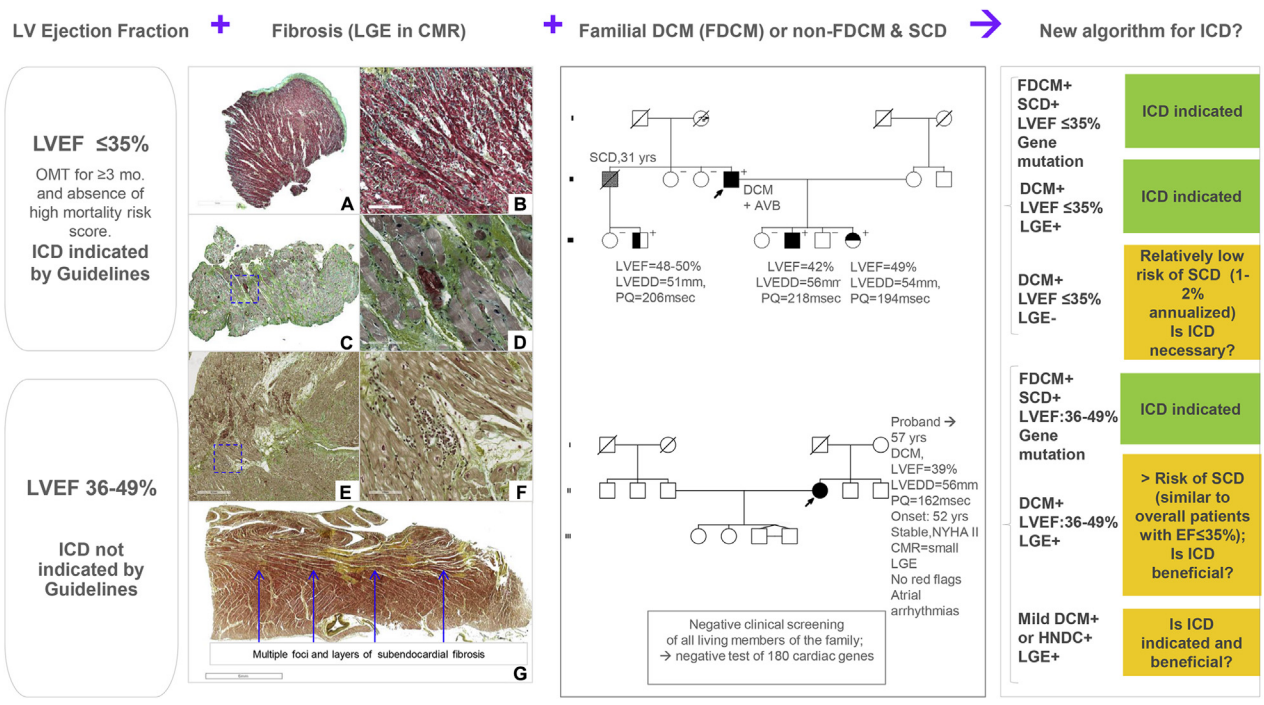
The arrhythmic endpoint occurred in 350 patients, 21% of LGE-positive versus 4.7% of LGE-negative patients with annual event rates of 6.9% and 1.6%, respectively. The pooled odds ratio for arrhythmic endpoint was 4.3 (95% confidence interval: 3.3 to 5.8) in the total population and maximal in the subgroup of studies that included only patients for primary prevention ICD (odds ratio: 7.8; 95% confidence interval: 1.7 to 35.8). The investigators concluded

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the [a]Centre for Inherited Cardiovascular Diseases, IRCCS Foundation, University Hospital Policlinico San Matteo, Pavia, Italy; [b]Department of Cardiology, Santa Chiara Hospital, Healthcare Research and Innovation Program, PAT-FBK, Trento, Italy; and the [c]Icahn School of Medicine at Mount Sinai Hospital, New York, New York. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

FIGURE 1 The Possible Polyparametric Integration of Criteria Selectively Useful for Clinical Decision Making Regarding Implantable Cardioverter-Defibrillator Therapy for Primary Prevention of Sudden Cardiac Death in Patients With Nonischemic Dilated Cardiomyopathy



The **2 left panels** summarize the indications for implantable cardioverter-defibrillator (ICD) implantation in primary prevention, according to current guidelines. The **pathology panels** show a spectrum of myocardial fibrosis in nonischemic dilated cardiomyopathy (DCM): **A and B** are low- and high-magnification views of and endomyocardial biopsy from a patient with dilated cardiolaminopathy; **C and D** are low- and high-magnification views of dilated cardiotroponinopathy and single-myocyte necrosis; **E and F** are low- and high-magnification views of a myocardial sample from the heart of a patient with dilated cardiodystrophinopathy and focal myocardial inflammation; **G** is a low-magnification view of a left ventricular wall sample from a previously asymptomatic and unrecognized patient who died suddenly. **A to F** show some of the different patterns of interstitial fibrosis, likely detectable by cardiac magnetic resonance (CMR) in **C to F** and likely undetectable in **(A)** and **(B)**. The true diagnostic resolution of CMR is one of the key issues to be resolved to prevent or limit underestimation of mild interstitial fibrosis. The **pedigree panels** show 2 paradigmatic examples of DCM: familial, autosomal-dominant dilated cardiolaminopathy **(top)** and nonfamilial, sporadic DCM **(bottom)**. The **right panel** highlights the conditions in which ICD therapy is indicated **(green-filled cells)** and those in which ICD therapy may not be currently indicated by guidelines but probably needs revision **(yellow-filled cells)** (modified with permission from Disertori et al. [11]). AVB = atrioventricular block; FDCM = familial dilated cardiomyopathy; HNDC = hypokinetic nondilated cardiomyopathy (as described by Pinto et al. [9]); LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LGE = late gadolinium enhancement; NYHA = New York Heart Association; OMT = optimal medical therapy; SCD = sudden cardiac death.

that LGE was a strong independent predictor of arrhythmic events and could improve risk stratification for SCD and appropriateness of ICD therapy. The ability of LGE on CMR for the detection of myocardial fibrosis is supported by extensive evidence, including histological confirmation. In DCM, the remodeling process is characterized by changes in the extracellular matrix and interstitial fibrosis (**Figure 1**). The fibrous tissue constitutes a substrate for ventricular arrhythmias that induces slow and heterogeneous conduction, favors re-entrant circuits, and produces vulnerability to life-threatening ventricular tachyarrhythmias. In their meta-analysis, Di Marco et al. (4) considered a dichotomous categorization of patients on the basis of LGE-verified presence or absence of fibrosis, rendering it practically applicable for a widespread clinical use. The arrhythmias may originate from the heterogenous distribution of fibrous tissue including patchy, focal, diffuse or perimyocytic (both viable and nonviable) patterns. The amount of ventricular fibrosis can influence a dose-response effect, with an increase of arrhythmic risk related to the increasing extent of fibrosis. Although heterogeneity and the extent of fibrosis have been studied, particularly in post-infarction patients, some studies have shown a correlation with arrhythmias also in nonischemic DCM patients (3,5). These prospective observational studies with appropriate follow-up periods offer a reasonable body of evidence in favor of using LGE for ICD implantation in nonischemic